GUIDELINES FOR Leucovorin DOSAGE AND ADMINISTRATION DO NOT ADMINISTER Leucovorin INTRATHECALLY		
Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromo-molar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micrommolar at 72 hours, and more than 0.05 micromolar 96 hours after administration	Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Normal Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administeation e.g., an increase from 0.5 mg/dl to a leavel of 1 mg/dl or more).	150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate Leucovorin therapy, these patients require continuing hydration and urinary alkalization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which aresignificant butless severethan abnormalities described in the table above These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, Leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medication which interact with methotrexate (e.g., medications which may interfere with methotrexate elimaination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicites are observed.

Impaired Methotrexate Elimination or Inadvertent Over dosage

Leucovorin rescue should begin as soon as possible after an inadvertent over dosage and within 24 hours of methotrexate administration when there is a delayed excretion (see WARNINGS section). Leucoverin 10 mg/m2 should be administered IM, IV,or PO every 6 hours until the serum methotrexate level is less than 10-8 M. in the presence of gastrointestinal toxicity, nausea, or vomiting, Leucovorin should be administered parenterally. Do not administer Leucocorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. if the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than $5x10^{-6}$ M or the 48 hour level is greater than 9×10^{-7} M, the dose of Leucovorin should be increased to 100 mg/m2 IV every 3 hours until the methotrexate level is less than 10^{-8} M.

Hydration (3 L/D)and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Megaloblastic Anemia Due to Folic Acid Deficiency

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Because of the calcium content of the Leucovorin solution, no more than 160 mg of Leucovorin should be injected intravenously per minute (16 ml of a 50mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Leucovorin should not be mixed in the same infusion as 5-fluorouracil, since this may lead to the formation of a precipitate.

Presentation:

Leucovorin Calcium Injection IP(Calcium Folinate Injection IP), 50mg/mL, is supplied in sterile, single use vials

Store below 30ºC. Protect from light.

Marketed by:
NEOVA BIOGENE PRIVATE LIMITED
Monte Plaza, Malviya Marg,
Mulund (w), Mumbai-80, India

Manufactured in India by:
BETA DRUGS LTD.
Kharuni-Lodhimajra Road, Vil. Nandpur,
Baddi, Distt Solan, Himachal Pradesh-173205

OLVORIN 50mg

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

℞

Leucovorin Calcium Injection IP

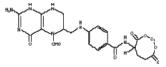
(Calcium Folinate Injection IP)

Each ml contains:

Calcium Folinate	IP	
Eq. to Folinic Acid		50mg
Methylparaben	IP	0.08% w/v
Propylparaben	IP	0.02% w/v
Water for Injections	IP	q.s.

Description

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists. Also known as folinic acid, Citrovorum factor, or 5-formy 1-5,6,7,8-tetreahydrofolic acid, this compound has the chemical designation of Calcium N - [p-(6RS) -2 - amino - 5 - formyl - 5,6,7,8 - tetrahydro -4 - hydroxy - 6 -pteridiny1] methyl] amino]benzoyl] - L-glutamate (1:1) The structural formula of Leucovorin calcium is:



$C_{20}H_{21}CaN_7O_7$ M.W.=511.51

Leucovorin Calcium Injection IP (Calcium Folinate Injection IP)is a sterile preparation, with preservative indicated for intramuscular (IM)or intravenous (IV) administration. Each mL contains Leucovorin calcium IP equivalent to Leucovorin,50mg; *There is 0.004 mEq of calcium per mg of Leucovorin. Solution contains no bacteriostat or antimicrobial agents.

Clinical Phatmacology: Leucovorin is a mixture of the diastereoisomers of the 5-formy1 derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-1 isomer, known as Citrovorum factor or (-)-folinic acid. Leucovorin does not requier reduction by the enzyme dihydrofolate reducatase in order to paeticipate in reactions utilzing folates as a source of "one-carbon" moieties.

1- Leucovorin (1-5-formyltetrehydrofolate)is rapidly metabolized (via 5, 10-methenyltetrahydrofolate then 5, 10-methylenetetrahydrofolate) to 1,5-methyltetrahydrofolate. 1,5-Methyltetrahydrofolate can in turn be metabolized via other pathways back to 5,10-methyltetrahydrofolate. which is converted to 5-methyltetrahydrofolate by an irreversible, enzyme catalyzed reduction using the cofactors FADH2 and NADPH. Administration of Leucovorin can counterac the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, Leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of Leucovorin does not appear to alter the Plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10 mthylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzym. The pharnacokinetics after intravenous, intramuscular and oral administration of a 25 mg dose of Leucovorin were studied in male volueers. After intravenous administrstion, serum total reduced folates (as measured by Lactobacillus casei assay) reached a mean peak of 1259 ng/ml (range 897 to 1625).The mean time to peak was 10 minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by Streptococcus faecalis assay) which rose to 1206 ng/ml at 10 minutes. A sharp drop in parent compound followed and coincided with the appearance of the active metabolite 5-methy 1-THF which became the predominant circulating form of the drug. The mean peak of 5-methy1-THF was 258 ng/ml and occurred at 1.3 hours. The terminal half-life for total reduced folstes was 6.2 hours. Thearea umder the concentration versus time curves (AUGs) for 1-Leucovorin, d-Leucovorin and 5-methyltetrahydrofolate were 28.4 ± 3.5, 956 ± 97 and 129 ± 12 (mg/min/L ± S.E.). When a higher dose of d,1-Leucovorin(200 mg/m2) was used, similar results were obtained. The d-isomer persisted in plasma at concentrations greatly exceeding those of the 1-isomer. After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/ml (range 240 to 725) and occurred at 52 minutes. Similar to IV administration, the initial shar rise was due to the parent compound. The mean peak of 5-formyl- THF was 360 ng/ml and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference of statidtical significance between IM and IV administration in the AUC for total reducd folates, 5-formyl-THF, or 5-methyl-THF. After oral administration of Leucovorin reconstituted with aromatic elixir, the mean peak concentration of derum total reduced folates was 393 ng/mL (range 160 to 550). The mean time to peak was 2.3 hours and the terminal half-life was 5.7 hours. The major component was the metabolite 5-methylitetrahydrofolate to which Leucovorin is primarily converted in the intestinal mucosa. The mean peak of 5-methyl-THF was 367 ng/mL at 2.4 hours. The peak level of the parent compound was 51 ng/mL at 1.2 hours. The AUC of total reduced folates after oral administration of the 25 mg dose was 92% of the AUC after intravenous asministration.

In a randomized clinical study conducted by the Mayo Clinic and the North Central Cancer Treatment Group (Mayo/NCCTG) in patients with advanced metastatic colorectal cancer three treatment reginens were compared: Leucovorin (LV)200 mg/m^2 and 5- fluorouracil (5-FU)370 mg/m^2 versus LV 20 mg/m^2 and 5-FU 425 mg/m^2 versus 5-FU 500 mg/m^2 All drugs were administered by slow intravenous infusion daily for 5 days repeated every 28 to 35 days.Response rates were 26%(p=0.04 versus 5-FU alone),43% (p=0.001 versus 5-FU alone) and 10% for the high dose Leucovorin, low dose Leucovorin and 5-FU alone groups respectively. Respective median survival times were 12.2 months (p=0.037), 12 months (p=0.050), and 7.7 months. The low dose LV regimen gave a statistically significant improvement in weight gain of more than 5%, relief of symptoms, and improvement in performance status. The high dose LV regimen gave a statistically significant improvement in performance status and trended toward improvement in weight gain and in relief of symptoms but these were not statistically significant.

In a second Mayo/NCCTG randomized clinical study the 5-FU alone arm was replaced by a regimen of sequentially administered methotrexate (MTX), 5-FU, and LV. Response rates with LV 200 mg/m2 and 5-FU 370 mg/m2 versus LV 20 mg/m2 and 5-FU 425 mg/m2 versus sequential MTX and 5-FU and LV were respectively 31%(p=<.01),42%(p=<.01), and 14% Respective median survival times were 12.7

months (p=< 04), 12.7 months (p=<.01), and 8.4 months. No statistically significant difference in weight gain of more than 5% or in improvrmrnt in performance status was seen between the treatment arms:.

Indications and Usage

Leucovorin calcium is indicated after high dose methotrexate therapy in osteosarcoma Leucovorin calciaum is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists. Leucovorin calcium is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible. Leucovorin is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. Leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

Contraindications

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B12. A hematologic remission may occur while neurologic manifestations continue to progress.

Warnings

In the treatment of accidental over dosages of folic acid antagonists, intravenous Leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate) and Leucovorin rescue increases, Leucovorin's effectiveness in counteracting toxicity decreases. In the treatment of accidental overdosages of intrathecally adminstered folic acid antagonists, do not adminster Leucovorin intrathecally. Leucovorin MAY BE HARMFUL OR FATAL IF GIVEN INTRATHECALLY. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with Leucovorin.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of Leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously. Because of the benzyl alcohol contained in certain diluents used for reconstituting Leucovorin Calcium for Injection, when doses greater than 10 mg/m^2 are administered Leucovorin Calcium for Injection should be reconstitiuted with sterile Water for Injection, IP, and used immediately (see DOSAGE AND ADMINISTRATION section). Because of the calcium content of the Leucovorin solution, no more than 160 mg of Leucovorin should be injected intravenously per minute (16mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of 5- fluorouracil must be lower than usually administered. Although the toxicities observed in patients treated with the comobination of Leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients trwated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more servere and of prolonged duration in patients treated with the combination. In the first Mayo/NCCTG controlled trial, toxicity, primarily gastrointestinal, resulted in 7% of patients requiring hospitalzation when treated with 5-fluorouracil alone or 5-fluorouracil in combination with 200mg/m2 of Leucovorin and 20% when treated with 5-fluorouracil in combination with 20 mg/m2 of Leucovorin. In the second Mayo/NCCTG trial, Hospitalizations related to treatment toxicity also appeared to occur more often in patients treated with the low dose Leucovorin/5-fluorouracil combination than in patients treated with the high dose combination 11% versus 3% Therapy with Leucovorin and 5-fluorouracil must not be Initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have complrtely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In an additional study utilizing higher weekly doses of 5-fluorouracil and Leucovorin, elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.[1]

Seizures and/or syncope have been reported rarely in cancer patients receiveng Leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors, however, a causal relationship has not been established. The concomitant use of Leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo- controlled study.

Precautions

General

parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit and not absorb theLeucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney. Since Leucovorin enhances the toxicity of fluorouracil, Leucovorin/5-fluorouracil combination therapy for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of anti-metabolite cancer chemotherapy. Particular care should be taken in the treatment of elderly or debilitated colorectal cancer patients, as these patients may be at increased risk of sever toxicity.

Laboratory Tests

Patients being treated with the Leucovorin/5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses a CBC with differential and platelets has to be repeated weekly and thereafter once each cycle at the time of anticipated WBC nadir. Electrolytes and liver function tests should be performed prior to each treatment for the three cycles then prior to every other cycle. Dosage modifications of fluorouracil should be instituted as follows, based on the most severe toxicities:

Diarrhea and/or Stomatitis	WBC/mm3 Nadir	Platelets/mm3 Nadir	5-FU dose
Moderate	1,000 - 1,900	25-75,000	decrease 20%
Severe	<1,000	<25,000	decrease 20%

If no toxicity occurs, the 5-fluorouracil dose may increase 10% Treatment should be deferred until WBCs are 4,000/mm3 and platelets 130,000/mm3. If blood counts do not reach these levels within two weeks, treatment should be discontinued. Patients should be followed up with physical examination prior to each treatment course and appropriate radiological examination as needed. Treatment should be discontinued when there is clear evidence of tumor progression.

Drug Interactions

Folic acid in large amounts may counteract the anti-epileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in suseptible pediatric patients.

Preliminary animal and human studies have shown that small quantities of systemically administered Leucovorin enter the CSF primarliy as 5-methyltetrahyfrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of Leucovorin may reduce the efficacy of intrathecally administered methotrexate. Leucovorin may enhance the toxicity of 5-fluorouracil (see WARNINGS section).

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adequate animal reproduction studies have not been conducted with Leucovorin. It is also not known whether Leucovorin can cause fetal harm when administered to a pregnant woman or can effect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Leucovorin is administered to a nursing mother.

Pediatric Use

See PRECAUTIONS, Drug Interactions subsection.

Adverse Reactions

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral Leucovorin. No other adverse reactions have been attributed to the use of Leucovorin per se.

The following table summarizes significant adverse events occurring in 316 patients treated with the Leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for advanced colorectal carcinoma. These data are taken from the Mayo/NCCTG large muliticenter prospective trial evaluating the efficacy and safety of thecombination regimen.

PERCENTAGE OF PATIENTS TREATED WITH Leucovorin/FLUOROURACIL FOR ADVANCED COLORECTAL CARCINOMA REPORTING ADVERSE EXPERIENCES OR HOSPITALIZED FOR TOXICITY

*
High LV = Leucovorin 200 mg/m2
†
Low LV = Leucovorin 20 mg/m2
‡
Any = percentage of patients reporting toxicity of any severity
§
Grade 3+ = percentage of patients reporting toxicity of Grade 3 or higher

	(High LV*) /5-FU		(Low LV†) /5-FU		5-FU Alone	
	(N=155)		(N=161)		(N=70)	
	Any‡	Grade 3+ §	Any‡	Grade 3+ §	Any‡	Grade 3+ §
	(%)	(%)	(%)	(%)	(%)	(%)
Leukopenia	69	14	83	23	93	48
Thrombocytopenia	8	2	8	1	18	3
Infection	8	1	3	1	7	2
Nausea	74	10	80	9	60	6
Vomiting	46	8	44	9	40	7
Diarrhea	66	18	67	14	43	11
Stomatitis	75	27	84	29	59	16
Constipation	3	0	4	0	1	-
Lethargy/Malaise/Fatigue	13	3	12	2	6	3
Alopecia	42	5	43	6	37	7
Dermatitis	21	2	25	1	13	-
Anorexia	14	1	22	4	14	-
Hospitalization for Toxicity	5%		15%		7%	

Over dosage

Excessive amounts of Leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

Dosage and Administration

Advanced Colorectal Cancer

Eithe of the following two regimens is recommended:

1. Leucovorin is administered at 200mg/m2 by slow intravenous injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370mg/m2 by intravenous injection.
2. Leucovorin is administered at 20 mg/m2 by intravenous injection followed by 5-fluorouracil at 425 mg/m2 by intravenous injection.

5-Fluorouracil and Leucovorin should be administered separately to avoid the formation of a precipitate. Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4 week(28 day) intervsls, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely recovered from the toxic effects of the prior treatment course. In subsequent treatment course, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of 5- fluorouracil should be reduced by 20% for patients who experienced moderate hematologic or gastrointestinal toxcity in the prior treatment course, and by 30% for patients who experienced sever toxicity (see PRECAUTIONS: Laboratory Tests). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10% Leucovorin dosages are not adjusted for toxicity. Several other doses and sehedules of Leucovorin/5-fluorouracil therapy have also been evaluated in patients with advanced colorectl cancer: some of these alternative regimens may also have efficacy in the treatment of this diseas. However, further clinical research will be required to confirm the safety and effectiveness of these alternative Leucovoring/5-fluorouracil treatment regimens.

Leucovorin Rescue After High-Dose Methotrexate Therapy

The recommendations for Leucovorin rescue are based on a methotrexate dose of 12 to 15 grams/m2 administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information).4 Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, Leucovorin should be adminstered parenterally.

Do not administer Leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10-8 M (0.05 micromolar). The Leucovorin dose should be adjusted or Leucovorin rescue extended based on the following guidelines: